American Journal of Hematology 55:134–138 (1997)

Analysis of Intramedullary Cell Density by MRI Using the Multiple Spin-Echo Technique

Akira Masumoto,[1]* Shuji Yonekura,[1] Munetaka Haida,[2] Noriharu Yanagimachi,[3] and Tomomitsu Hotta[1]

[1]Fourth Department of Internal Medicine, Tokai University School of Medicine, Kanagawa, Japan
[2]Department of Neurology, Tokai University School of Medicine, Kanagawa, Japan
[3]Department of Diagnostic Radiology, Tokai University School of Medicine, Kanagawa, Japan

Analysis of the intramedullary cell distribution by magnetic resonance imaging (MRI) using conventional techniques involves subjectively interpreting images and estimating the cell distribution on the basis of signal intensity characteristics. In recent years, attempts have been made to achieve more precise analysis by new techniques, including chemical shift imaging. The multiple spin-echo (MSE) technique offers some advantages over conventional MRI. Since it allows measurement of the transverse magnetization decay curve at 32 or more points, it is capable of separating several tissue components with different relaxation times. In addition, this technique can be used with MRI instruments having a static magnetic field as low as 1.0 Tesla. In the present study, the intramedullary cell density was assessed by MRI using the MSE technique in 4 patients with aplastic anemia (AA), 4 patients with myelodysplastic syndrome (MDS), and 5 normal subjects. The water component of the marrow (with a short relaxation time) and the fat component (with a long relaxation time) were separated from each other by analyzing MR images obtained using the MSE technique, and the signal intensity ratio of the 2 components was calculated. The ratio was significantly higher in the AA group than in the other groups (AA vs. MDS, *P* = 0.0209, AA vs. normal controls, *P* = 0.0143). The present technique appears promising for quantitative assessment of the intramedullary cell density. Am. J. Hematol. 55:134–138, 1997. © 1997 Wiley-Liss, Inc.

Key words: multiple spin-echo technique; MRI; intramedullary cell density; AA; MDS

INTRODUCTION

Magnetic resonance imaging (MRI) is a useful noninvasive technique for assessing the distribution of marrow cells over a by far wider region than is possible by marrow aspiration and biopsy [1]. However, analysis of MR images acquired by conventional techniques is based on subjective assessment of differences in signal intensity and image pattern characteristics [2–4]. In addition, there are cases that cannot be assessed by conventional techniques. Attempts have been made to overcome these difficulties by developing new techniques such as chemical shift imaging (CSI) [5–7]. However, these new techniques can only be employed at large institutions, for they require instruments with a magnetic field of 1.5 Tesla or more.

If the intramedullary tissues can be separated into two components, i.e., the hemopoietic cells (composed largely of water) and the fatty tissue, the ratio of these two components provides a more objective indicator of the intramedullary cell distribution [8]. The multiple spin-echo (MSE) technique measures 32 points on the transverse magnetization decay curve and allows separation of intramedullary tissue components even when two or more spin-spin relaxation times (T_2) are present. In addition, this technique can be used with low-field strength instruments generating no more than 1.0 Tesla [9–11]. The present study investigated the feasibility of analyzing the intramedullary cell density by MRI using the MSE technique.

*Correspondence to: Akira Masumoto, M.D., Fourth Department of Internal Medicine, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa 259-11, Japan.

Received 28 September 1996; Accepted 12 February 1997

TABLE I. Hematological Date of Subjects

			Peripheral Blood Values			Bone Marrow Values		
Case no	Age	Sex	WBC(/μl)	Hb(g/dl)	PIt(/μl)	NCC[a](/μl)	Mybl[b](%)	Clinical Diagnosis
1	28	F	2,800	3.1	3,000	35,000	0.5	SAA[c]
2	21	F	2,200	5.1	22,000	20,000	0.2	SAA
3	43	M	2,800	6.9	12,000	12,000	—	AA
4	18	F	500	6.5	4,000	3,000	—	SAA
5	26	M	3,400	6.1	7,000	116,000	2.0	MDS (RA)
6	37	M	1,000	9.3	26,000	153,000	6.8	(RAEB)
7	27	F	2,200	3.3	15,000	190,000	5.4	(RAEB)
8	75	F	1,500	6.6	32,000	151,000	1.6	(RA)
9	32	M	6,100	15.6	192,000	N.D.	N.D.	Normal Control
10	32	F	7,900	14.4	204,000	N.D.	N.D.	Normal Control
11	31	M	5,700	17.1	179,000	N.D.	N.D.	Normal Control
12	31	M	6,400	16.0	246,000	N.D.	N.D.	Normal Control
13	32	M	7,500	15.2	238,000	N.D.	N.D.	Normal Control

[a]NCC: nucleated cell count.
[b]Mybl: Myeloblast.
[c]SAA: severe aplastic anemia.

MATERIALS AND METHODS

Subjects

Studies were carried out on 8 patients with hematological disorders causing pancytopenia, including 4 patients with aplastic anemia (AA) and 4 patients with myelodysplastic syndrome (MDS), as well as on 5 normal volunteers without any hematological disorders. The subjects had no diseases such as heart failure or active infection. Prior to entry into the study, informed consent was obtained from all the subjects. Hematological data on the subjects are given in Table I.

MRI

MRI was performed with a 1.0 Tesla instrument (Magnetom, Siemens, Erlangen, Germany). T_2 relaxation times for ^1H were measured by MSE using Carr-Purcell pulse sequences [12], with a 256′256 matrix, a pulse interval (2t) of 22.0 msec, 32 echo measurement points, an echo time (TE) of 22–518 msec, a repetition time (TR) of 5.0 sec, and a slice thickness of 5 mm. A saddle coil 30 cm in diameter was used for radiofrequency communication. MRI studies were performed on all lumbar vertebrae by obtaining median sagittal scans.

Calculation of T_2

Images with various TEs were obtained by MRI. To increase the reliability of the images, the third lumbar vertebra, located at the center of the saddle coil, was selected as the target. The region of interest was set in the bone marrow of this lumbar vertebra, and the mean signal intensity of the pixels within this region was determined for each TE. The value thus obtained was considered to represent the mean level of transverse magnetization of the target for each TE. The transverse magnetization decay curve was plotted logarithmically and represented the mean transverse magnetization value for each TE determined at 32 points. Then the slope of the curve was fitted to linear models by the least squares procedure and the T_2 iteration technique to calculate the values of the two T_2 components.

Calculation of the Intramedullary Fat/Water Ratio

The intramedullary fat/water ratio was calculated from the two T_2 components as the signal intensity ratio using the following equation.

$$A = MoF \exp(-t/T_2F) + MoS \exp(-t/T_2S)$$

where, A is the amplitude of spin-echo signals, MoF is the amplitude of the fast component at $t = 0$, MoS is the amplitude of the slow component at $t = 0$, and t is the sampling time.

$$\text{Fat ratio (\%)} = \frac{MoS}{MoF + MoS}$$

This relationship is shown in Figure 1. Data were assessed by the Mann-Whitney U-test, and $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Table I shows that the AA group (cases 1–4) had pancytopenia and hypoplastic marrow without any morphological abnormalities of the other blood cells.

The MDS group (cases 5–8) featured pancytopenia and normocellular marrow with trilineage morphological abnormalities, such as pseudo-Pelger-Hüet cells, Giant platelets, micromegakaryocytes, and megaloblasts.

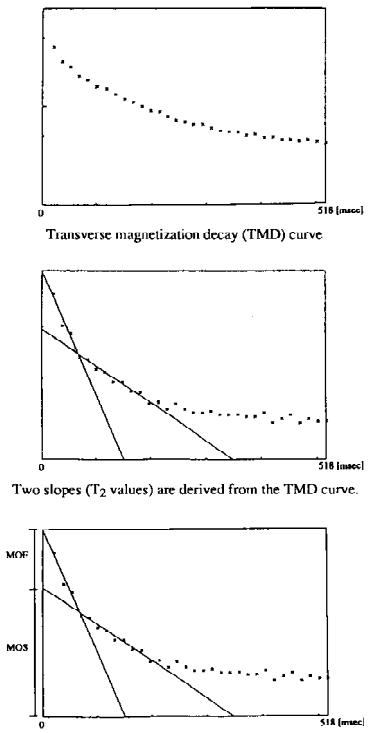

Fig. 1. Schematic representation of the procedure for determining the fat component ration from T_2 values derived from the TMD curve.

The transverse magnetization decay curve was not linear, but showed a gentle slope in all cases (Fig. 1). This means that there were at least 2 components with different slopes. The slope was fitted to a linear model by the least squares procedure to obtain the values of the two T_2 components (Table II).

Patients with AA were treated with various combinations of anabolic steroids, anti-thymocyte globulin, antilymphocyte globulin, cyclosporine-A, methylprednisolone, recombinant human granulocyte colony-stimulating factor (rhG-CSF, Filgrastim), and blood transfusion.

Patients with MDS were also treated with various combinations of prednisolone, fluoxymesterone, ubenimex, and rhG-CSF (Filgrastim) in combination with chemotherapy (etoposide, cytosine arabinoside, cytarabine ocfosfate, etc.) or differentiation inducers (alfacalcidol, all-trans retinoic acid, 13-cis retinoic acid, etc.).

The normal control group (cases 9–13) had normal peripheral blood findings and did not undergo bone marrow aspiration for ethical reasons and because of the low likelihood of abnormalities in the marrow.

As shown in Table II, there were two T_2 components, a fast component (T_2F) and a slow component (T_2S). The T_2F value was 76.77 ± 10.84 (msec) for the AA group, 70.27 ± 4.76 for the MDS group, and 73.56 ± 9.12 for the healthy control group, so there was no significant difference in T_2F among the three groups. The T_2S value was 133.58 ± 10.66 (msec) for the AA group, 130.91 ± 16.97 for the MDS group, and 115.81 ± 10.22 for the normal control group, so there was also no significant difference among the three groups. The T_2F values were consistent with previously reported data [13] for intramedullary hemopoietic cells, and the T_2S values were consistent with previously reported values [13,14] for fatty tissue.

TABLE II. T_2 Values of two Components of Individual Subjects

Case No.	T_2F (msec)	T_2S (msec)	$M_0S/(M_0F + M_2S)$ (%)
1	69.95	130.02	68.472
2	75.25	129.40	76.414
3	92.54	149.31	78.009
4	69.30	125.61	67.420
	76.77 ± 10.84	133.58 ± 10.66	72.579 ± 5.406[a]
5	70.44	149.87	52.020
6	65.55	110.34	41.765
7	76.74	138.03	58.479
8	68.34	125.41	42.106
	70.27 ± 4.76	130.91 ± 16.97	48.592 ± 8.128
9	73.71	130.75	43.500
10	88.98	113.25	51.612
11	67.30	116.33	44.743
12	66.42	102.14	57.789
13	71.37	116.56	43.893
	73.56 ± 9.12	115.81 ± 10.22	48.307 ± 6.247

[a]Values are mean ± SD.

These results suggested that the T_2F value represents hemopoietic cells in the bone marrow, while the T_2S value represents fatty tissue. When the intramedullary fat/water ratio was calculated for all subjects, it was significantly higher in the AA group than in the normal control group ($P = 0.0143$) and the MDS group ($P = 0.0209$) (Fig. 2). There was no significant difference between the MDS and normal control groups.

DISCUSSION

Being a noninvasive technique, MRI allows investigation of a far wider region when used for the analysis of intramedullary cell density, unlike bone biopsy and aspiration which provide details about a very small part of the bone marrow. In addition, MRI can be repeated as often as necessary. It may, therefore, be an excellent technique for prolonged follow-up, in particular.

MRI is generally done by acquiring T_1-weighted images [2–4] using spin-echo (SE) sequences or short T_1 inversion recovery (STIR) sequences [15], which suppress fat signals and enhance image contrast. However, these methods have the disadvantage that estimation of the intramedullary cell distribution is extremely subjective, because it depends on signal intensity patterns. Since the fat content of the intramedullary tissue increases with aging, imaging findings may vary with the age of an individual [16,17]. In addition, image interpretation requires a certain degree of skill. To find a more

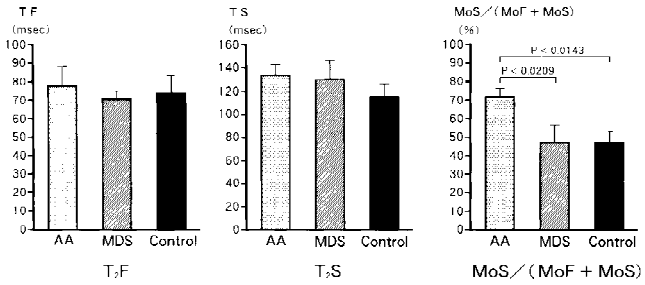

Fig. 2. Comparison of intramedullary tissue components among AA, MDS, and normal control groups.

Fig. 3. Lumbar vertebra visualized by MRI using the MSE method (Case 1: TR = 5.0 sec, TE = 38 msec).

objective approach to the assessment of intramedullary cellularity, attempts have been made to separate the intramedullary tissue into water and fat components and then compare the ratio of water to fat numerically. Methods using CSI [5,7] and spectroscopy [8,13] have been described previously. Although these methods provide useful information, their use is limited because they require special or expensive instruments. Thus, these methods are largely restricted to experimental use and can only be employed at large institutions. The nuclear magnetic resonance relaxation times obtained with MRI present some problems regarding reliability [18] because they are affected by scanning conditions if conventional techniques are used. However, Kurita et al. [19] compared relaxation times obtained by the MSE method with relaxation times obtained using MRI equipment for instrument analysis, and concluded that T_2 relaxation times obtained by the MSE method were reliable. The biggest advantage of this method is that reliable relaxation times can be obtained with ordinary low-field strength MRI instruments, i.e., it dispenses with the need for special equipment. The present communication appears to be the first report on an analysis of intramedullary cell density by this method.

The T_2S value (the slow component of the relaxation time) reflects the fat content of intramedullary tissue. It was 133.58 ± 10.66 (msec) for the AA group, 130.91 ± 16.97 for the MDS group, and 115.81 ± 10.22 for the healthy control group, and there was no significant difference among the three groups. These results were very close to the previously reported value of 113 ± 21 [13]. The T_2F value (the fast component of the relaxation time) reflects the water content of intramedullary tissue and was also close to the previously reported value of 71 ± 14 [13] for 5 normal controls in all groups in the present study. These results suggest that T_2 values obtained by the MSE method are sufficiently reliable for clinical use.

The ratio of MoS to all signals (MoF + MoS) reflects the fat content of intramedullary tissue. This ratio was significantly higher in the AA group than in the normal control and MDS groups, reflecting the fact that AA is associated with fatty marrow. In patients presenting with pancytopenia and hypoplastic MDS who lack notable morphological abnormalities of their red cells, it is often difficult to make a differential diagnosis between AA and MDS [20]. MRI using the MSE method allows a more objective assessment of the intramedullary cellularity than conventional image reading and thus may be helpful in the differentiation of such diseases.

In conclusion, we used the MSE technique to assess the bone marrow of patients with AA or MDS and normal controls. The fat/water signal intensity ratio was significantly higher in the AA group, which reflected the increase of intramedullary fat. Using this technique, we may be able to assess the condition of the bone marrow more objectively by separating the intramedullary cellular component from the fat component using the difference in T_2 values.

ACKNOWLEDGMENTS

For continuous encouragement and assistance during the course of this study, we are greatly indebted to Isao Muro (Department of Radiology, Tokai University Hospital), Daisaku Kurita (Department of Neurology, Tokai University School of Medicine), and Ryuki Fukuda (Department of Internal Medicine, Tokai University School of Medicine).

REFERENCES

1. Vogler JB III, Murphy WA: Bone marrow imaging. Radiology 168: 679–693, 1988.
2. Olson DO, Shields AF, Scheurich CJ, et al: Magnetic resonance imaging of the bone marrow in patients with leukemia, aplastic anemia, and lymphoma. Invest Radiol 21:540–546, 1986.
3. Stevens SK, Moore SG, Amylon MD: Repopulation of marrow after transplantation: MR imaging with pathologic correlation. Radiology 175:213–218, 1990.
4. Steiner RM, Mitchell DG, Rao VM, et al: Magnetic resonance imaging of bone marrow: Diagnostic value in diffuse hematologic disorders. Magn Reson Q 6:17–34, 1990.
5. Wismer GL, Rosen BR, Buxton R, et al: Chemical shift imaging of bone marrow: Preliminary experience. AJR 145:1031–1037, 1985.
6. Brateman L: Chemical shift imaging: A review. AJR 146:971–980, 1986.
7. McKinstry CS, Steiner RE, Young AT, et al: Bone marrow in leukemia and aplastic anemia: MR imaging before, during, and after treatment. Radiology 162:707–721, 1987.
8. Schick F, Einsele H, Bongers H, et al: Leukemic red bone marrow changes assessed by magnetic resonance imaging and localized ^{1}H spectroscopy. Ann Hematol 66:3–13, 1993.
9. Haida M, Yamamoto M, Matsumura H, et al: Intracellular and extracellular spaces of normal adult rat brain determined from the proton nuclear magnetic resonance relaxation times. J Cereb Blood Flow Metab 7:552–556, 1987.
10. Hazlewood FC, Change DC, Nichols BC, et al: Nuclear magnetic resonance transverse relaxation times of water protons in skeletal muscle. Biophys J 14:583–606, 1974.
11. Shioya S, Haida M, Tsuji C, et al: Acute and repair stage characteristics of magnetic resonance relaxation times in oxygen-induced pulmonary edema. Magn Reson Med 8:450–459, 1988.
12. Carr HY, Purcell EM: Effects of diffusion on free precession in nuclear magnetic resonance experiments. Phys Rev 94:630–638, 1954.
13. Mulkern RV, Meng J, Oshio K, et al: Bone marrow characterization in the lumbar spine with inner volume spectroscopic CPMG imaging studies. JMRI 4:585–589, 1994.
14. Shioya S, Haida M, Ono Y, et al: Tissue characterization of pneumonia and irradiated rat lungs with magnetic resonance relaxation times. Magn Reson Imag 12:799–803, 1994.
15. Golfieri R, Baddeley H, Pringle JS, et al: The role of the STIR sequence in magnetic resonance imaging examination of bone tumours. Br J Rad 63:251–256, 1990.
16. Ricci C, Cova M, Kang YS, et al: Normal age-related patterns of cellular and fatty bone marrow distribution in the axial skeleton: MR imaging study. Radiology 177:83–88, 1990.
17. Moore SG, Dawson KL: Red and yellow marrow in the femur: Age-related changes in appearance at MR imaging. Radiology 175:219–223, 1990.
18. Pykett IL, Rosen BR, Buonanno FS, et al: Measurement of spin-lattice relaxation times in nuclear magnetic resonance imaging. Phys Med Biol 28:723–729, 1983.
19. Kurita D, Haida M, Shinohara S, et al: A fundamental study of ^{1}H relaxation times measured with MRI equipment: Comparison with NMR equipment for instrument analysis. J Physiol Soc Jpn 24:257–262, 1994.
20. Nand S, Godwin JE: Hypoplastic myelodysplastic syndromes. Cancer 62:958–964, 1988.